

## CARDIOVASCULAR MEDICINE

## Effects of congestive heart failure on plasma von Willebrand factor and soluble P-selectin concentrations in patients with non-valvar atrial fibrillation

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*Heart* 2005;91:759–763. doi: 10.1136/hrt.2004.036160

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Accepted 28 July 2004

**Objective:** To examine further the relations of plasma von Willebrand factor (vWf, an index of endothelial damage and dysfunction) and soluble P-selectin (sP-sel, an index of platelet activation) concentrations to the presence and onset of clinical congestive heart failure (CHF) and the degree of left ventricular (LV) dysfunction in patients taking part in the SPAF (stroke prevention in atrial fibrillation) study.

**Methods:** Plasma concentrations of vWf and sP-sel were measured by enzyme linked immunosorbent assay (ELISA) in 1321 participants in the SPAF III study and related to the presence and onset of clinical CHF, as well as echocardiographic findings. Of the 1321 patients with atrial fibrillation (AF), 331 (25%) had a documented history of clinical heart failure, of which 168 cases were related to a new or recurrent episode of acute decompensated heart failure occurring within the preceding three months.

**Results:** Mean plasma vWf was higher among patients with AF and CHF (154 (29) v 144 (31) IU/dl,  $p < 0.001$ ), particularly those with acute or recent decompensated symptoms. Patients with severe LV dysfunction on two dimensional echocardiography and low fractional shortening also had significantly higher vWf concentrations than those with no LV dysfunction. CHF patients with clinical features—with (156 (28) IU/dl) and without (152 (31) IU/dl) LV dysfunction—also had higher mean vWf concentrations than patients with asymptomatic LV dysfunction (146 (31) IU/dl,  $p < 0.001$ ). The presence of mitral regurgitation in CHF was associated with lower vWf concentrations. Plasma sP-sel concentrations were not affected by presence, onset, or severity of heart failure.

**Conclusions:** CHF may contribute to hypercoagulability and thrombotic risk in AF through increased endothelial damage and dysfunction. Patients with acute or recent decompensated features have the highest degree of endothelial damage and dysfunction. The presence of CHF clinical features was an important determinant of plasma vWf concentrations.

The risk of stroke and thromboembolism is substantially increased in the presence of non-valvar atrial fibrillation (AF), but if congestive heart failure (CHF) or moderate to severe left ventricular (LV) systolic dysfunction is also present, this risk is further increased two- to fourfold.<sup>1</sup> In these patients, the source of embolism is presumed to be mural thrombus formation in the left atrium (including the left atrial appendage, especially with concurrent AF)<sup>2,3</sup> or left ventricle.<sup>4</sup> Furthermore, the presence of dilated cardiomyopathy per se also predisposes to left atrial thrombus formation.<sup>5</sup>

Traditionally, abnormal stasis within the atria or ventricle in AF and CHF, respectively, has been thought to be the main cause of thrombogenesis. However, such abnormal flow is only one component of Virchow's triad of thrombogenesis—in recent years, abnormal haemostatic factors and platelets (abnormal blood constituents) and endothelial or endocardial abnormalities (abnormal vessel wall) have been recognised in both AF and CHF, fulfilling Virchow's triad.<sup>6–9</sup>

We recently reported plasma concentrations of von Willebrand factor (vWf, a marker of endothelial damage and dysfunction<sup>10</sup>) and soluble P-selectin (sP-sel, a marker of platelet activation<sup>11</sup>) in 1321 participants in the SPAF (stroke prevention in atrial fibrillation) III study in relation to stroke risk factors.<sup>12</sup> In the whole cohort, we found that recent CHF along with age, prior cerebral ischaemia, diabetes, and body mass index were independently associated with vWf and sP-sel concentrations. Furthermore, moderate to severe LV dysfunction was also associated with high vWf concentrations on univariate, but not multivariate, analysis of the

whole cohort of patients. In the longitudinal analysis, we found that among patients with AF receiving aspirin, raised concentrations of vWf (endothelial damage and dysfunction) were predictive of stroke and vascular events but raised sP-sel concentrations (platelet activation) were not associated with increased cardiovascular risk.<sup>13</sup> None the less, we were keen to examine further the relations of vWf and sP-sel concentrations to the presence and onset of clinical CHF and to the degree of LV dysfunction in the CHF subgroup of patients with AF taking part in the SPAF study. Indeed, whether the co-morbid presence of CHF (itself a risk factor for thromboembolism, even when in sinus rhythm) amplifies endothelial damage or dysfunction and platelet activation in patients with AF is uncertain.

## PATIENTS AND METHODS

Baseline venous samples from 1531 patients with non-valvar AF were collected. All patients were participants in SPAF III, which was performed at 20 clinical sites in the USA and Canada between 1993 and 1997; the design and main results have been reported previously.<sup>14</sup> Patients with any of four high risk criteria (women  $> 75$  years of age, systolic hypertension  $> 160$  mm Hg, impaired LV function (clinical heart failure within 100 days of entry or M mode fractional

**Abbreviations:** AF, atrial fibrillation; CHF, congestive heart failure; ELISA, enzyme linked immunosorbent assay; FS, fractional shortening; INR, international normalised ratio; LV, left ventricular; SPAF, stroke prevention in atrial fibrillation; sP-sel, soluble P-selectin; vWf, von Willebrand factor

shortening (FS)  $\leq 25\%$ ), and previous thromboembolism) were randomly assigned to receive either adjusted dose warfarin (target international normalised ratio (INR) 2–3) or fixed, low dose warfarin (target INR 1.2–1.5) plus aspirin 325 mg/day (termed combination treatment). Participants without any of the four specific risk factors received aspirin 325 mg/day alone. The risk stratification scheme has been clinically validated in several independent assessments.<sup>15</sup>

An earlier study of various haemostatic markers among the same cohort has been reported previously.<sup>16</sup> Blood samples were initially collected within 30 days of enrolment from all participants and subsequently after three months, 12 months, and annually thereafter. Participants enrolled and followed up at outlying clinics at which specimens could not be adequately processed were not included; thus, one or more samples were collected from 69% (1339 of 1936) of SPAF III participants for these analyses at baseline or after three months but, owing to natural sample wastage over time, only 1321 of these specimens were available for the present cross sectional analysis. The present study population characteristics are broadly similar to those of the SPAF clinical trial.<sup>14</sup>

### Blood collection and laboratory analysis

Blood collection materials were prepared at the Laboratory for Clinical Biochemistry Research, Department of Pathology, University of Vermont. Blood for vWf and sP-sel assays was drawn into 3.8% sodium citrate tubes (Becton Dickinson), immediately mixed by gentle inversion, stored on melting ice, and centrifuged at 4°C for 30 000 *g*-minutes within one hour of phlebotomy. Plasma was separated for vWf and sP-sel assays. sP-sel and vWf were measured by enzyme linked immunosorbent assay (ELISA) with reagents from R&D Systems (Abingdon, UK) and Dakopatts (Ely, UK), respectively. The unit for vWf is IU/dl and was standardised by reference vWf from the National Institute for Biological Standards and Controls, Blanche Lane, South Mimms, Potters Bar, Hertfordshire, UK. Intra-assay coefficients of variation for all ELISAs were  $< 5\%$  and interassay variances were  $< 10\%$ .

### Assessment of heart failure and LV (dys)function

Patients entering the SPAF study had heart failure and LV (dys)function defined at each clinical centre clinically and by echocardiography. Firstly, a documented history of (any) clinical CHF was used as a comparison with patients with no documented history of CHF. Of the patients with a history of clinical CHF, patients with a new or recurrent episode of acute decompensated CHF occurring within the preceding three months were compared with patients without such a history. Two dimensional and M mode echocardiography were performed at each study centre. M mode echocardiography was used to calculate FS. The severity of LV dysfunction on two dimensional echocardiography was classed as normal, mild, moderate, and severe and was based on the wall motion index according to the system suggested by the American Society of Echocardiography, as previously described.<sup>3</sup>

### Data analysis

Continuous data were analysed by the Shapiro-Wilks test to determine distribution. Normally distributed data are expressed as mean (SD). Differences in markers between groups were evaluated with two sample *t* tests and one way analysis of variance, as appropriate, with Tukey's post hoc test for intergroup comparisons. Non-parametric data (sP-sel) were determined with normality test and expressed as median (interquartile range). Differences in markers were evaluated with Mann Whitney U and Kruskal-Wallis tests as appropriate. Forward and backward stepwise linear

regression analyses were used to identify features independently associated with marker concentrations. Statistical analyses were undertaken with SPSS software (SPSS Inc, Chicago, Illinois, USA). Significance was accepted at the 0.05 level (two sided).

## RESULTS

Of the 1321 patients with AF, 331 (25%) had a documented history of clinical heart failure, of which 168 cases were related to a new or recurrent episode of acute decompensated heart failure occurring within the preceding three months. Echocardiography found normal systolic function in 144 patients with heart failure, and 137 patients with AF not known to have clinical heart failure had underlying LV dysfunction (termed asymptomatic LV dysfunction). Patients with AF with heart failure did not have a higher frequency of prior cerebral ischaemia (transient ischaemic attack or stroke), although there was a higher proportion of other comorbid illnesses (table 1).

### Relation of vWf and sP-sel to presence and onset of clinical heart failure

Patients with clinical heart failure had higher mean vWf ( $p < 0.001$ ), but not sP-sel ( $p = 0.7$ ), concentrations than patients with AF without heart failure (table 1). Among patients with heart failure, those with acute or recent decompensated symptoms (in the previous three months) had higher mean plasma vWf concentrations ( $p = 0.002$ ) than patients with chronic stable disease, possibly corresponding with lower FS ( $p = 0.001$ ) in the decompensated heart failure group (table 2(a)).

### Relation of vWf and sP-sel to LV dysfunction

When patients were categorised according to severity of LV dysfunction on two dimensional echocardiography (normal, mild, moderate, and severe), the combined group with moderate and severe LV dysfunction had higher mean vWf than did patients with AF with normal function ( $p = 0.002$ ) (table 2(b)). Patients with severe LV dysfunction also had significantly lower mean FS and systolic and diastolic blood pressures than did the others (that is, normal, mild, and moderate LV dysfunction).

Patients were also divided into quartiles based on mean FS calculated on M mode echocardiography. FS data were available for 1198 of 1321 patients. Mean vWf in the first two quartiles (higher FS) were lower than in the next two quartiles (lower FS) ( $p < 0.001$ ) (table 2(c)). Mean age, systolic and diastolic pressures, and sP-sel concentrations were comparable across subgroups.

### Relation of vWf and sP-sel to clinical heart failure and LV dysfunction

Lastly, we compared patients classified according to presence of clinical heart failure, presence of LV systolic dysfunction on two dimensional echocardiography, both or neither. Patients with both clinical heart failure and LV dysfunction (HF/dysfunction) had the lowest mean FS and blood pressures. Mean vWf in the HF/dysfunction group was highest compared with patients with AF with neither heart failure nor LV dysfunction (non-HF/normal) and with the asymptomatic LV dysfunction group (table 2(d)). Patients with clinical heart failure but normal systolic function (HF/normal) also had significantly higher vWf than did the non-HF/normal group ( $p = 0.03$ ) despite comparable FS. In contrast, the asymptomatic LV dysfunction group did not differ in plasma vWf from the HF/normal ( $p = 0.3$ ) and non-HF/normal ( $p = 0.9$ ) groups despite a significantly lower FS.

**Table 1** Baseline clinical characteristics of 1321 patients with non-valvar atrial fibrillation

	With clinical HF	Without clinical HF	p Value
Number	331	990	
Age (years)	70 (10)	69 (9)	0.3
Men	226 (68%)	716 (72%)	0.2
Medical history			
Prior cerebral ischaemia	69 (21%)	170 (17%)	0.1
Hypertension	217 (66%)	529 (53%)	<0.001
Diabetes mellitus	75 (23%)	121 (12%)	<0.001
Peripheral vascular disease	40 (12%)	58 (6%)	<0.001
Prior MI	89 (27%)	72 (7%)	<0.001
Angina	74 (22%)	102 (10%)	<0.001
CABG	62 (19%)	98 (10%)	<0.001
Drug treatment at time of blood sampling			
ACE inhibitor	218 (66%)	197 (20%)	<0.001
Loop diuretic	233 (70%)	96 (10%)	<0.001
Warfarin	232 (70%)	381 (39%)	<0.001
Aspirin	159 (48%)	636 (64%)	<0.001
Smoking history (former + current)	195 (58%)	587 (59%)	0.9
Systolic BP (mm Hg)	136 (20)	137 (20)	0.4
Diastolic BP (mm Hg)	76 (11)	79 (10)	0.001
LV dysfunction on two dimensional echocardiography			<0.001
Normal	144 (44%)	853 (86%)	
Mild	59 (18%)	98 (10%)	
Moderate	58 (17%)	33 (3%)	
Severe	70 (21%)	6 (1%)	
FS (%)	28 (11)	37 (8)	<0.001
Left atrial diameter (cm)	5.0 (0.8)	4.6 (0.7)	<0.001
Regurgitation	251 (76%)	598 (61%)	<0.001
vWf (IU/dl)	154 (29)	144 (31)	<0.001
sP-sel (ng/ml)	32 (26–40)	32 (25–41)	0.7

Parametric data are expressed as mean (1 SD) and compared by two sample *t* test. Dichotomous variables are expressed as absolute number (percentage) and compared by  $\chi^2$ . Non-parametric data are expressed as median (interquartile range) and compared by Mann Whitney U test.

BP, blood pressure; CABG, coronary artery bypass grafting; FS, fractional shortening determined on M mode echocardiography; HF, heart failure; LV, left ventricular; MI, myocardial infarction; sP-sel, soluble P-selectin; vWf, von Willebrand factor.

### Correlations and multivariate analyses

Among patients with AF with clinical heart failure, plasma vWf was higher in those with diabetes (table 3(a)). For patients with AF with heart failure, an association was found between plasma vWf and advancing age (Pearson  $r = 0.14$ ,  $p = 0.01$ ) and plasma sP-sel ( $r = 0.11$ ,  $p = 0.04$ ). In a multivariate analysis examining 19 variables, recent decompensated symptoms ( $p = 0.007$ ), diabetes ( $p = 0.009$ ), sP-sel ( $p = 0.03$ ), and advancing age ( $p = 0.006$ ) were independently associated with increasing plasma vWf in patients with AF with CHF ( $r^2_{\text{adjusted}} = 0.07$ ). For the 168 patients with acute or recent heart failure, no further increases in mean vWf were noted with co-morbidities, but mitral regurgitation was associated with lower plasma concentrations (157 (30) v 169 (29) IU/dl,  $p = 0.04$ ).

Median plasma sP-sel concentrations of patients with CHF were higher among current and past smokers and those with peripheral vascular disease and prior myocardial infarction; a trend was found for diabetes. Patients with prior cerebral ischaemia (stroke and transient ischaemic attacks) tended to have lower sP-sel concentrations (table 3(b)).

### DISCUSSION

vWf is one of several endothelium derived haemostatic mediators, with key roles in platelet aggregation and stabilisation of circulating clotting factors.<sup>17</sup> Large quantities of vWf are stored in the Weibel-Palade bodies of endothelial cells and can be mobilised rapidly after endothelial cell activation<sup>18</sup> to result in transient increases of plasma vWf.<sup>10</sup> In experimental models at least, endothelial dysfunction has been shown to promote thrombosis, vasospasm, and vessel occlusion.<sup>19</sup> One recent study found increased concentrations of immunoreactive vWf in the endothelium over the endocardial cells lining the surface of human left atrial

appendage in patients with cardiac disease and further found thrombus formation over sites exhibiting impaired endothelial function.<sup>20</sup>

Thus, persistently increased concentrations of vWf and endothelial damage and dysfunction pose a real risk to thrombosis. Indeed, our recent cross sectional study suggests a relation between vWf and risk stratification for stroke and thromboembolism in AF.<sup>12</sup> Furthermore, our survival analysis of 994 patients with AF found that plasma vWf concentrations were a significant predictor of both stroke and vascular events, with greatest risk at highest concentrations.<sup>13</sup> Following adjustment for other clinical predictors, the relation between vWf and stroke became non-significant but vWf remained an independent predictor of vascular events.<sup>13</sup>

In this study, we have shown that clinical CHF substantially increases plasma vWf concentrations in patients with AF and appears to exert more influence over severity of endothelial damage and dysfunction than underlying LV dysfunction. This is further supported by the fact that plasma vWf is highest among patients with acute or recent decompensated CHF, deemed a particularly high risk subgroup for AF related strokes in the SPAF trial patient population,<sup>21</sup> although more recent analyses have not reported CHF to be a risk factor.<sup>22–23</sup> Of note, none of the other co-morbid diseases in the present study subgroup resulted in further increases in vWf concentrations.

Clinical heart failure is a syndrome characterised by failure of cardiac output to meet the metabolic demands of tissues in the body, which then triggers a host of compensatory mechanisms to support circulation. Neurohormonal stimulation, one of the main compensatory mechanisms, has been known to cause impaired endothelial function.<sup>24–25</sup> Other pathophysiological states induced in CHF that are likely to

**Table 2** Relation of vWf and sP-sel to HF in patients with atrial fibrillation

(a) Relation to presence of stable and recent decompensated clinical HF					
	Chronic stable HF		Decompensated HF (in past 3 months)		p Value
Number	163		168		
Age (years)	69 (10)		71 (10)		0.1
FS (%)	30 (11)		26 (12)		0.001
Systolic BP (mm Hg)	136 (19)		135 (22)		0.5
Diastolic BP (mm Hg)	77 (11)		76 (10)		0.3
vWf (IU/dl)	149 (27)		159 (31)		0.002
sP-sel (ng/ml)	32 [26–40]		32 [25–41]		0.9
(b) Relation to underlying LV dysfunction by two dimensional echocardiography					
	Normal LV function	Mild dysfunction	Moderate dysfunction	Severe dysfunction	p Value
Number	997	157	91	76	
Age (years)	70 (9)	70 (9)	67 (12)	68 (10)	0.06
FS (%)	38 (8)	29 (7)	23 (8)	17 (5)	<0.001
Systolic BP (mm Hg)	137 (20)	137 (22)	137 (22)	124 (18)	<0.001
Diastolic BP (mm Hg)	78 (10)	78 (11)	77 (11)	74 (10)	0.005
vWf (IU/dl)	145 (31)	148 (30)	152 (30)	156 (29)	0.004
sP-sel (ng/ml)	33 [25–41]	33 [26–41]	31 [27–39]	33 [26–39]	0.9
(c) Relation to quartiles of FS calculated by M mode echocardiography (n = 1198)					
	Quartile				p Value
	1st	2nd	3rd	4th	
Number	323	313	270	292	
Age (years)	70 (9)	69 (10)	69 (10)	68 (10)	0.06
FS (%)	46 (4)	37 (2)	32 (2)	22 (5)	
Systolic BP (mm Hg)	139 (20)	135 (19)	137 (20)	135 (23)	0.09
Diastolic BP (mm Hg)	78 (10)	78 (10)	78 (10)	77 (11)	0.7
vWf (IU/dl)	143 (33)	144 (30)	150 (31)	150 (30)	0.006
sP-sel (ng/ml)	32 [25–40]	33 [26–41]	32 [25–40]	32 [26–40]	0.9
(d) Relation to clinical HF and the degree of LV (dys)function by two dimensional echocardiography					
	No HF and normal LV function	Asymptomatic LV dysfunction	Clinical HF		p Value
			Normal systolic function	LV dysfunction	
Number	853	137	144	187	
Age (years)	69 (9)	69 (10)	72 (9)	69 (10)	0.03
FS (%)	38 (7)	28 (7)	37 (9)	22 (8)	<0.001
Systolic BP (mm Hg)	137 (20)	136 (22)	139 (18)	133 (22)	0.02
Diastolic BP (mm Hg)	79 (10)	78 (11)	77 (11)	76 (11)	0.004
vWf (IU/dl)	144 (31)	146 (31)	152 (31)	156 (28)	<0.001
sP-sel (ng/ml)	33 [25–41]	31 [25–40]	31 [23–40]	32 [26–40]	0.6

Parametric values are expressed as mean (1 D) and compared by two sample *t* tests or one way analysis of variance. Non-parametric values are expressed as median (interquartile range) and compared by Mann Whitney U test or Kruskal Wallis test.

affect endothelial cell function are inflammation and oxidative stress.<sup>26</sup> In contrast, the presence of mitral regurgitation is associated with lower plasma vWf. This is perhaps not unexpected, as several studies have found a lower incidence of thrombus formation and embolism in patients with heart failure who previously had mitral regurgitation.<sup>27–30</sup> Indeed, if the decreased thrombus formation in mitral regurgitation may be caused by the stirring effect of the blood pool in the left atrium, then we can hypothesise that a localised endocardial disturbance may prevail, as CHF may well promote more local endothelial damage and dysfunction (for example, by atrial dilatation and distension) rather than as a generalised condition in the entire vasculature.

Unlike vWf, the presence, onset, and severity of heart failure and LV dysfunction had no further effect on plasma sP-sel in patients with AF. One reason may be that platelet activation is more important to thrombogenesis found at sites of high shear stress, such as that occurring in the initial stages of arterial thrombosis,<sup>31</sup> than to intracardiac thrombus formation where low shear stress predominates.<sup>5–29</sup> This

would concur with findings in this study of increased sP-sel in patients with peripheral vascular disease and myocardial infarction. Some sP-sel is also released from activated endothelial cells, which may result in the association between sP-sel and vWf concentrations.<sup>32</sup>

This analysis is limited by its cross sectional nature and the lack of a sinus rhythm control group. However, previous studies looking at patients with either AF or heart failure have found plasma vWf and sP-sel to be increased in both groups compared with healthy volunteers in sinus rhythm.<sup>8–33</sup> The present analysis is the largest series examining vWf and sP-sel in patients with AF and concomitant CHF or LV dysfunction. Furthermore, the true pathogenetic mechanisms of thrombogenesis in AF and CHF are likely to be more complex than the two aspects studied in the present report—indeed, whether endothelial damage or dysfunction (as expressed by an increased vWf) is local (in the left atrium, for example) or generalised in patients with AF and CHF also remains uncertain.

In conclusion, clinical CHF influences plasma concentrations of vWf in AF and may add to the risk of intracardiac

**Table 3** Comparison of plasma markers by associated co-morbidity in 331 patients with atrial fibrillation and HF

(a) vWf (IU/dl) with and without co-morbidity			
Co-morbid factors	Co-morbidity		p Value
	Present	Absent	
Men	153 (29)	155 (31)	0.7
Age >75 years	157 (26)	153 (31)	0.2
Ever smoked	154 (27)	153 (33)	0.7
Prior cerebral ischaemia	155 (27)	154 (30)	0.8
Hypertension	155 (29)	152 (30)	0.3
Diabetes mellitus	162 (30)	152 (29)	0.007
Peripheral vascular disease	161 (25)	153 (30)	0.09
Prior MI	154 (26)	154 (31)	0.9
Mitral regurgitation	153 (29)	156 (31)	0.6

  

(b) sP-sel (ng/ml) with and without co-morbidity			
Co-morbid factors	Co-morbidity		p Value
	Present	Absent	
Men	33 (26–41)	30 (23–39)	0.1
Age >75 years	31 (25–39)	33 (26–40)	0.2
Ever smoked	33 (26–42)	30 (23–39)	0.03
Prior cerebral ischaemia	31 (23–38)	33 (26–41)	0.05
Hypertension	32 (25–40)	34 (26–41)	0.3
Diabetes mellitus	34 (28–42)	31 (25–40)	0.06
Peripheral vascular disease	37 (29–45)	32 (25–39)	0.03
Prior MI	34 (28–44)	32 (25–39)	0.03
Mitral regurgitation	32 (25–41)	31 (26–39)	0.8

vWf is expressed as mean (1 SD) and compared by two-sample *t* test.

sP-sel is expressed as median (interquartile range) and compared by Mann Whitney U test.

thrombosis and strokes through its effects on endothelial damage and dysfunction. Patients with acute or recent decompensated CHF features have the highest degree of endothelial damage and dysfunction and the presence of clinical heart failure features was an important determinant of vWf concentrations.

## ACKNOWLEDGEMENTS

The SPAF-III investigators are listed in reference 21. We acknowledge the support of the Dowager Countess Eleanor Peel Trust and the City Hospital Research and Development programme.

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